Issues Surrounding Genetic Testing

Public Health Assessment of Genetic Tests for Screening & Prevention

September 26, 2004

Linda A. Bradley, PhD

Office of Genomics & Disease Prevention, CDC

Why Is Genetic Testing a Public Health Issue?

GeneTests

Diagnosis / prenatal diagnosis
- Mainly rare, single-gene disorders
- Chromosome abnormalities

Newborn screening

Other population-based applications
- Carrier detection
- Predictive testing
- Pharmacogenomics

Potential for broad public health impact

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ASHG Statement on Cystic Fibrosis Screening - 1990

- Offer carrier testing to couples with family history
- Pilot programs - gather more data on laboratory, educational, & counseling aspects of screening
- Address quality control in labs conducting tests
- Begin large-scale population screening when
  - the test detects a larger proportion of CF carriers
  - more information is available on issues surrounding the screening process

Routine CF carrier testing of pregnant women and other individuals is NOT yet the standard of care in medical practice

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Institute of Medicine

Committee on Assessing Genetic Risks

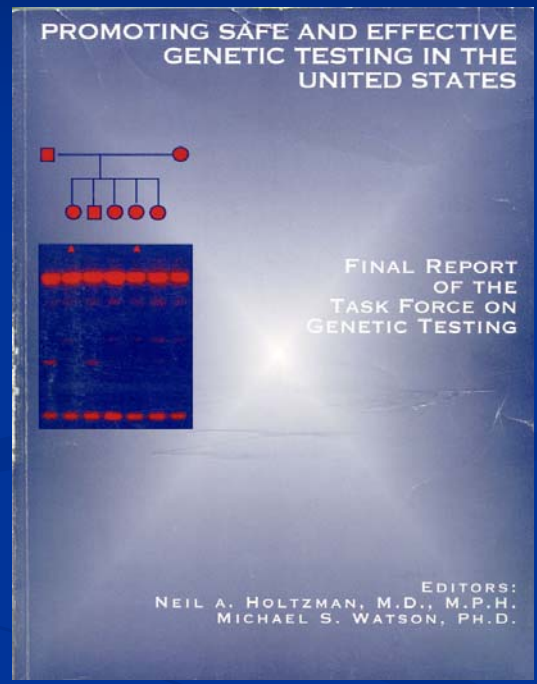
- 1994 Report: *Assessing genetic risks: Implications for health and social policy*
- Concerns raised:
  - Imperfect predictability of tests
  - Quality of labs providing clinical genetic tests
  - Lack of proven interventions for many disorders
  - Limited ability of many health care providers to explain genetic tests accurately and in a non-directive manner

NIH-DOE Task Force on Genetic Testing

- Launched April, 1995 to examine questions about genetic testing:
  - How will safety, effectiveness, and correct interpretation be ensured?
  - How accurate is genetic testing at identifying mutations?
  - How reliable is a positive test result as a predictor of disease?
  - How will the quality of laboratories providing the tests be ensured?
  - What are the psychological effects of genetic testing?
  - What counseling services are needed for informed decision-making?

NIH-DOE Task Force on Genetic Testing

- "For the most part, genetic testing in the US has developed successfully…"
- Evidence-based entry of new genetic tests into clinical practice
- The need to monitor laboratory performance



Final report, 1997 - http://www.nhgri.nih.gov/ELSI/TFGT_final/

NIH-DOE Task Force on Genetic Testing

Proposed definition of a ‘genetic test’

“Analysis of DNA, RNA, proteins and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes or karyotypes for clinical purposes.”

NIH-DOE Task Force on Genetic Testing

- Proposed assessment criteria
  - Analytic validity must be determined before entry into clinical practice
  - Data to establish clinical validity must be collected
    - Independently replicated and peer reviewed
    - Study sample representative of population to be tested
  - Before general acceptance in clinical practice, data must demonstrate benefits & risks (clinical utility)
- Raised issue of direct-to-consumer marketing
- Calls upon the Secretary HHS to establish an advisory committee on genetic testing

Secretary's Advisory Committee on Genetic Testing

- Convened in June, 1999
- Assess, in consultation with the public, the adequacy of current oversight of genetic testing
- Major issues addressed included:
  - Reviewing the options for oversight of genetic tests
  - Determining the process that should be used to collect, evaluate and disseminate data on tests
  - Selecting criteria for assessing the benefits and risks of tests

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Secretary's Advisory Committee on Genetic Testing - 2001 Report

- Confirmed Task Force criteria
- Added emphasis on "social issues" (ELSI)
- Encouraged collaboration between labs & Dept of Health & Human Services agencies to
  - facilitate data collection
  - provide information to providers & consumers
- Recommended
  - review of new genetic tests by FDA prior to marketing
  - augmenting Clinical Laboratory Improvement Act (CLIA) to ensure quality of genetic testing laboratories

http://www4.od.nih.gov/oba/sacgt.htm

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Secretary's Advisory Committee on Genetic Testing

Proposed definition of a 'genetic test'

"... an analysis performed on human DNA, RNA, genes, and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes, or karyotypes that cause or are likely to cause a specific disease or condition. A genetic test also is the analysis of human proteins and certain metabolites, which are predominantly used to detect heritable or acquired genotypes, mutations, or phenotypes."

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More recently

2003 SACGT disbanded

Secretary's Advisory Committee on Genetics, Health and Society (SACGHS)

Help address complex medical, ethical, legal and social issues raised by the application of new genetic technologies

2004 Notice of Proposed Rule Making for Genetic Testing Specialty under CLIA

Professional organizations, FDA, other agencies, and regulatory groups continue to consider their roles in evaluation and oversight of genetic testing

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Genetic testing issues

- Translating research to quality testing in clinical practice
- Providing information on appropriate use to providers, policy makers and the public
- Monitoring use and ensuring appropriate quality and access
- Addressing complex social issues
- Maintaining adequate oversight

Genetic tests: Current US oversight

Food and Drug Administration (FDA)

- Regulates test kits as *in vitro* diagnostic devices (IVDs)
  - Premarket review to assess accuracy & clinical sensitivity/ specificity
- Most genetic testing does not use commercial test kits
  - Two kits currently have FDA approval
- FDA has not regulated tests as clinical services, but regulation remains an option
- Controls ASRs (Analytic Specific Reagents) as medical devices
  - Good Manufacturing Practices, distribution, labeling
  - Laboratory responsible for validation

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Genetic tests: Current US oversight

Centers for Medicare & Medicaid Services

- Regulate all clinical laboratory testing performed on humans in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA)
- Laboratories develop clinical genetic tests under “home brew” regulations
  - Developed in house and marketed as clinical laboratory services
  - Labs responsible for analytic & clinical validation of tests
- Address personnel qualifications, quality control, proficiency testing

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Genetic tests: Current US oversight

State laws

- New York Clinical Laboratory Evaluation Program – process that oversees validation and approval of molecular tests

Professional organizations

- Clinical & laboratory practice guidelines
  - Expert opinion ± systematic evidence review

Public health assessment of genetic testing

Evidence-based evaluation needed at two key points:

- Transition from research to clinical practice
  - Evidence-based review to establish safety and efficacy before widespread use
- Post-implementation period
  - Demonstrate acceptable performance in practice
  - Assess implementation success and public health impact

Transition to clinical practice

- Collect and analyze data
  - Establish test performance
  - Begin assessment of benefits and risks
    - Avoid conflicts of interest
- Determine availability of needed facilities and resources
- Identify ethical, legal & social issues
- Develop plans for quality assurance, provider and consumer education, monitoring performance in practice
- Determine what we know and what we don’t know

Transition to clinical practice

- Summarize and disseminate findings
  - Educate providers & consumers
    - Realistic expectations
    - Appropriate use of tests
  - Guide policy development
    - Move from expert opinion to evidence-based review as a basis for practice guidelines & recommendations
  - Identify research priorities

Genetic testing: Different than non-genetic testing?

- Genetic information
  - May predict future health status
  - Can divulge information about family members
  - Can be used to discriminate/stigmatize
  - Can cause psychological harm
- Genotyping may only be done once
- Increased awareness of genetic testing and public perception that is “different”
  - Call for action

Genetic testing: Different than non-genetic testing?

- Evaluation process is the same
- "Handle with caution" (Green & Botkin, Ann Int Med, April 2003) any test that
  - Identifies a stigmatizing disease
  - Provides results that substantially affect family members
  - Identifies a disorder/condition for which there are no acceptable and effective treatments/actions
  - Has complex results that are difficult for clinicians to interpret

	USPSTF	ACCE Model
Goals	Assess merit of preventive measures (screening tests) Identify research agenda	Evaluate genetic tests before transition into clinical practice Identify gaps in knowledge
Methodology	Analytic framework with key questions that link preventions with outcomes Outcome tables on benefits and harms Focus on clinical utility	44+ targeted questions on ACCE elements plus disorder/ setting Collect, analyze, summarize data using tables & graphics Broader focus – "first look" at all elements
Grading Quality of Evidence	Structured approach for inclusion/exclusion	Ad hoc approach for extracting maximum information
Product	Specific recommendations about use in primary care	Review & interpret data without suggesting policy

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International health technology assessment (HTA)

Australia	Medical Services Advisory Committee
Canada	Health Canada
	Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
	Agence d'evaluation des technologies et des modes d'intervention en sante (AETMIS)
Denmark	Danish Centre for Evaluation & HTA
France	Agency for National Accreditation & Evaluation in Health
New Zealand	New Zealand HTA Clearing House
United Kingdom	National Coordinating Centre for HTA

HTAi	Health Technology Assessment International
INAHTA	International Network of Agencies for HTA

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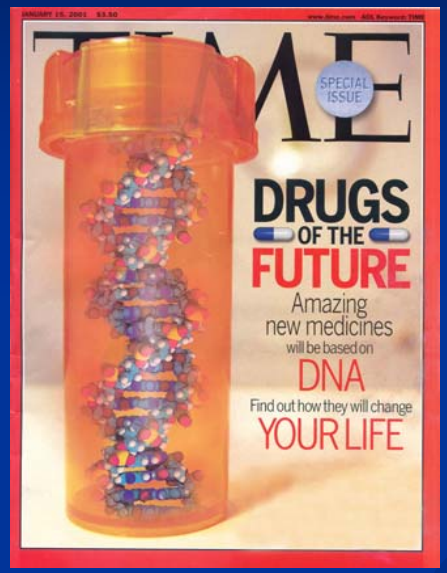
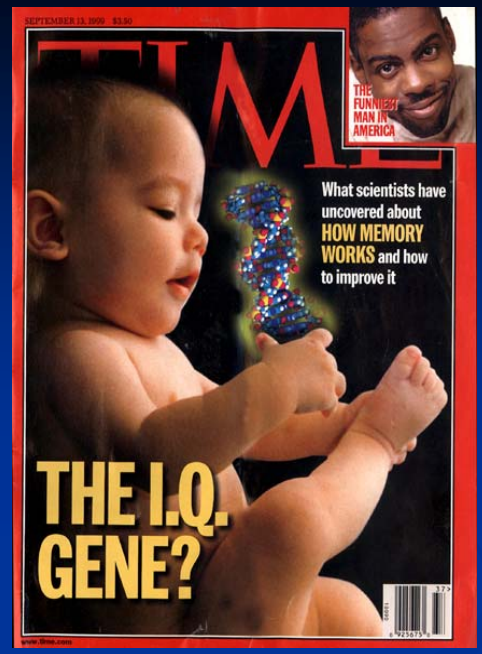
Expectation vs Hype





Genomics in medical practice in 2010?

Results of genetic testing in a hypothetical patient

Condition	Genes	RR	Lifetime
Prostate cancer	*HPC1, 2, 3*	0.4	7%
Alzheimer's	*APOE, FAD3, XAD*	0.3	10%
Heart disease	*APOB,CETP*	2.5	70%
Colon cancer	*FCC4, APC*	4.0	23%
Lung cancer	*NAT2*	6.0	40%

Adapted from: Collins FC, New Engl J Med 1999;341:28-37.

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Genomics in medical practice in 2004?

GENOVATIONS™

Predictive Genomics for Personalized Medicine

Great Smokies Diagnostic Laboratory

www.genovations.com/profiles.html

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Genovations™ Profiles

LAB TESTS
- Getting Started
- Order Kits
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CardioGenomic™Profile
Identifies genetic single nucleotide polymorphisms associated with increased risk of developing atherosclerosis, hypertension, and coronary artery disease. Risk factors include methylation defects, hyper-coagulation syndromes, cholesterol regulation defects, inflammation, general risk markers and cardio-protective markers.

OsteoGenomic™Profile
Identifies genetic single nucleotide polymorphisms associated with increased risk of developing osteopenia and osteoporosis. Risk factors include collagen synthesis, calcium metabolism, vitamin D3 activity, parathyroid hormone action, osteoclastic activity, and chronic inflammation.

DetoxiGenomic™Profile Now Available
Identifies genetic single nucleotide polymorphisms associated with increased risk of developing detoxification defects especially with increased exposure to xenobiotics and other toxins. Risk factors include altered cytochrome P-450 activity in phase 1 detoxification, impaired glutathione conjugation and acetylation in phase 2 reactions, altered catecholamine methylation and increased oxidative stress. Detoxification defects have been associated with increased risk for certain cancers, chronic fatigue, multiple chemical sensitivity, and alcoholism.

ImmunoGenomic™Profile
Identifies genetic single nucleotide polymorphisms associated with increased risk of developing defects in immune competence and surveillance. Risk factors include altered interleukin production and activity within the body and increased production of other cytokines like tissue necrosis factor alpha that may lead to conditions characterized by chronically up-regulated inflammatory response. Immunologic polymorphisms have been associated with increased risk of asthma, atopy, osteopenia, heart disease, and infectious diseases.

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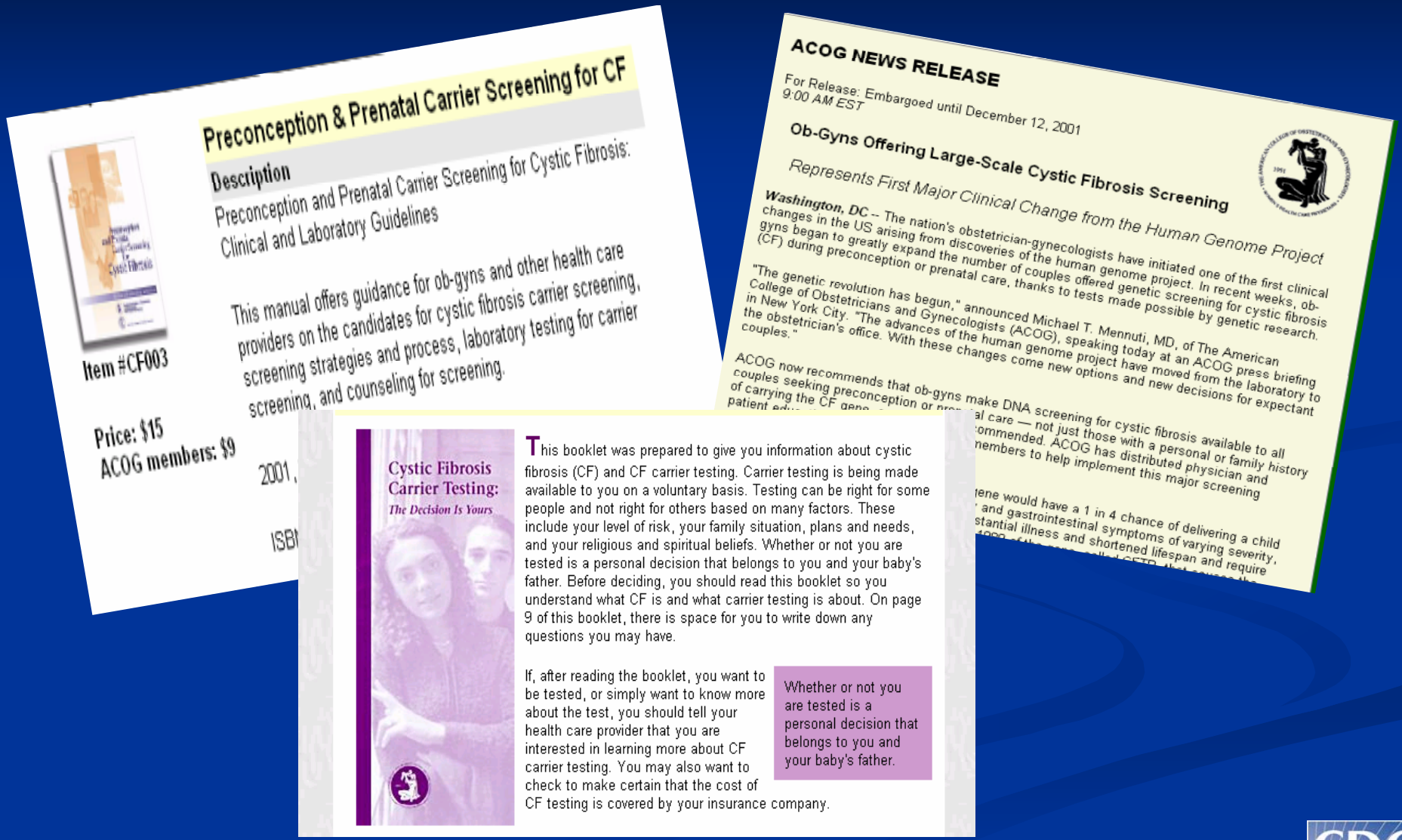
Cystic fibrosis carrier testing



Preconception & Prenatal Carrier Screening for CF

Description

Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and Laboratory Guidelines

This manual offers guidance for ob-gyns and other health care providers on the candidates for cystic fibrosis carrier screening, screening strategies and process, laboratory testing for carrier screening, and counseling for screening.

Item #CF003

Price: $15
ACOG members: $9

2001,

ISBN

ACOG NEWS RELEASE

For Release: Embargoed until December 12, 2001
9:00 AM EST

Ob-Gyns Offering Large-Scale Cystic Fibrosis Screening

Represents First Major Clinical Change from the Human Genome Project

Washington, DC -- The nation's obstetrician-gynecologists have initiated one of the first clinical changes in the US arising from discoveries of the human genome project. In recent weeks, ob-gyns began to greatly expand the number of couples offered genetic screening for cystic fibrosis (CF) during preconception or prenatal care, thanks to tests made possible by genetic research.

"The genetic revolution has begun," announced Michael T. Mennuti, MD, of The American College of Obstetricians and Gynecologists (ACOG), speaking today at an ACOG press briefing in New York City. "The advances of the human genome project have moved from the laboratory to the obstetrician's office. With these changes come new options and new decisions for expectant couples."

ACOG now recommends that ob-gyns make DNA screening for cystic fibrosis available to all couples seeking preconception or prenatal care — not just those with a personal or family history of carrying the CF gene.

ommended. ACOG has distributed physician and
nembers to help implement this major screening

ene would have a 1 in 4 chance of delivering a child
and gastrointestinal symptoms of varying severity,
stantial illness and shortened lifespan and require

This booklet was prepared to give you information about cystic fibrosis (CF) and CF carrier testing. Carrier testing is being made available to you on a voluntary basis. Testing can be right for some people and not right for others based on many factors. These include your level of risk, your family situation, plans and needs, and your religious and spiritual beliefs. Whether or not you are tested is a personal decision that belongs to you and your baby's father. Before deciding, you should read this booklet so you understand what CF is and what carrier testing is about. On page 9 of this booklet, there is space for you to write down any questions you may have.

If, after reading the booklet, you want to be tested, or simply want to know more about the test, you should tell your health care provider that you are interested in learning more about CF carrier testing. You may also want to check to make certain that the cost of CF testing is covered by your insurance company.

Whether or not you are tested is a personal decision that belongs to you and your baby's father.

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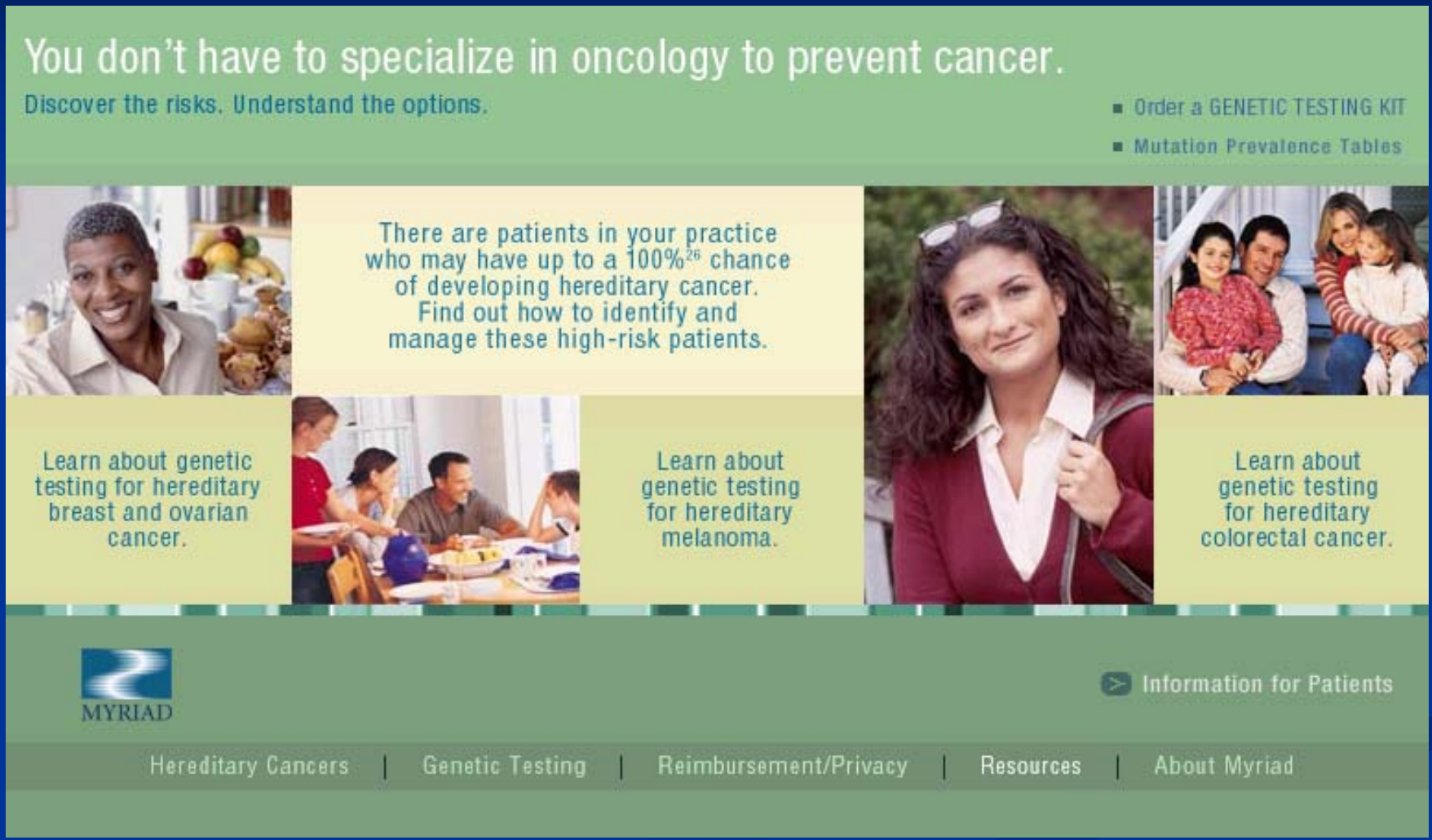
BRCA 1/2 Testing



Alternative for colorectal cancer screening

PreGen-Plus™
Non-Invasive Colorectal Cancer Screening

The Best Test Is the One That Gets Used

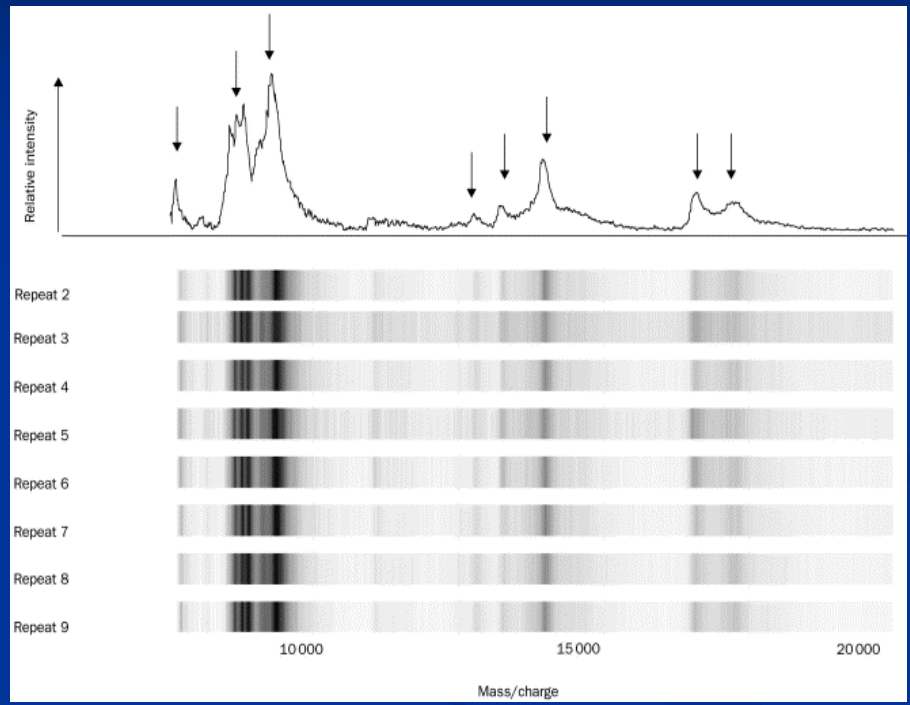
- Only 37% of colorectal cancers are detected at an early stage, when most treatable.[1]
- At least 60% of the 80 million Americans over the age of 50 have never been screened.[2]
- 30,000 lives could be saved annually if colorectal cancers were detected at an early stage.[3]

LabCorp is pleased to announce the availability of PreGen-Plus, a non-invasive test designed to detect clinically significant colorectal neoplasia (invasive cancer and advanced adenomas). PreGen-Plus is intended for use in asymptomatic patients 50 years of age and older who are at average risk of developing colorectal cancer.*

PreGen-Plus is Simple and Non-Invasive

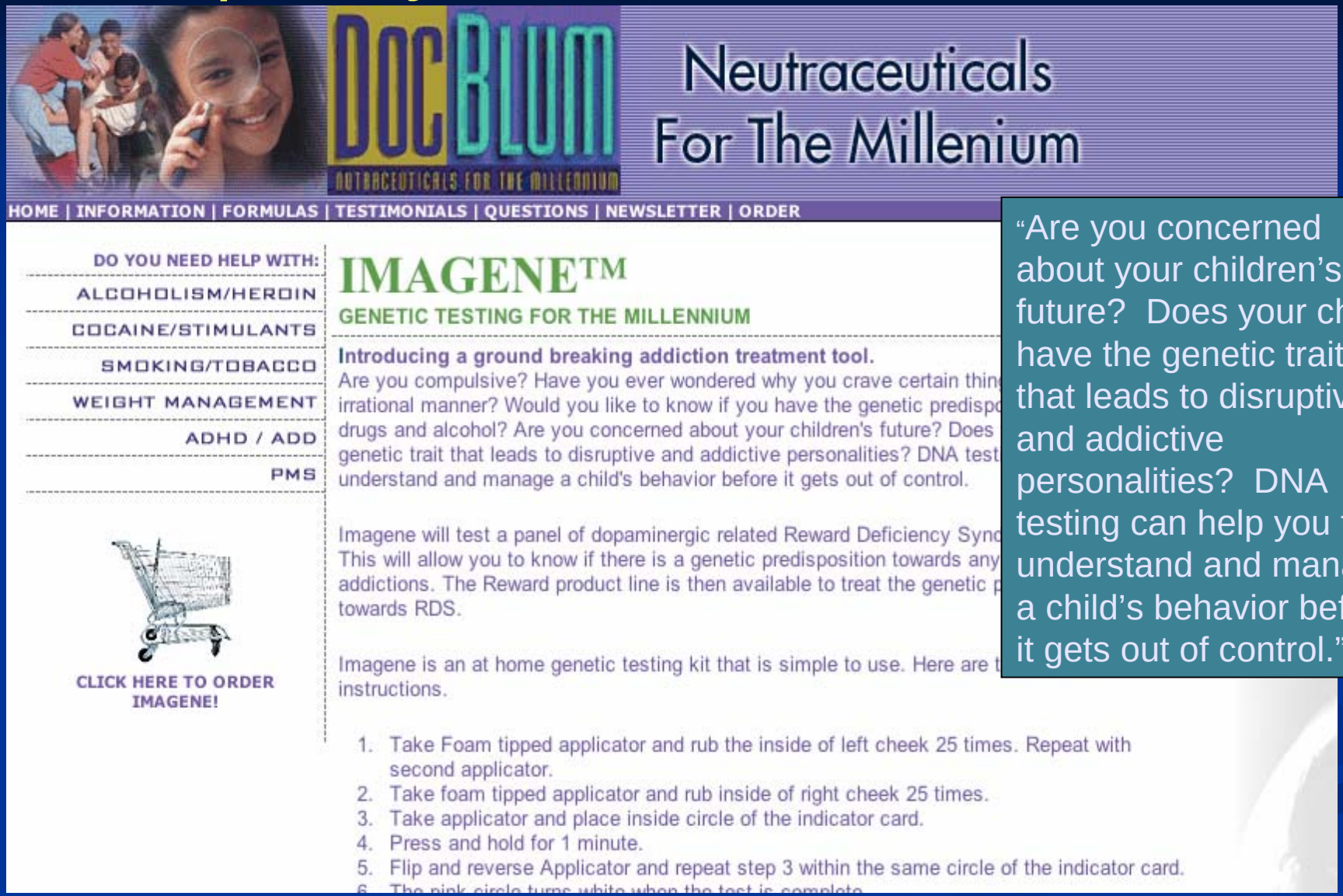
Diagnosing ovarian cancer by proteomics

- Patterns of specific serum proteins can be used to detect OvCa, even in early stages
- Clinical trials in progress
- FDA review will follow
- “OvaCheck” technology & interpretive software licensed
- Scheduled to be offered in 2004



Petricoin EF. Use of proteomic patterns in serum to identify ovarian cancer. Lancet. 2002 Feb 16;359(9306):572-7.

Susceptibility test for addictive behavior



"Are you concerned about your children's future? Does your child have the genetic trait that leads to disruptive and addictive personalities? DNA testing can help you to understand and manage a child's behavior before it gets out of control."